

EXHIBIT 18

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 November 2006 (09.11.2006)

PCT

(10) International Publication Number
WO 2006/119395 A3

- (51) International Patent Classification:
A61K 36/02 (2006.01) *A61P 31/00* (2006.01)
A61K 39/395 (2006.01) *A61P 35/00* (2006.01)
- (21) International Application Number:
PCT/US2006/017065
- (22) International Filing Date: 2 May 2006 (02.05.2006)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/677,212 3 May 2005 (03.05.2005) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/677,212 (CIP)
Filed on 3 May 2005 (03.05.2005)
- (71) Applicant (for all designated States except US):
BIOPOLYMER ENGINEERING, INC. [US/US];
3388 Mike Collins Drive, Eagan, Minnesota 55121 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **KAREL, Steven, J.** [US/US]; 1562 Park Circle, Mendota, Minnesota 55118 (US).
- (74) Agent: **ELRIFI, Ivor, R.**; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo PC, One Financial Center, Boston, Massachusetts 02111 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report: 18 May 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/119395 A3

(54) Title: COMBINATION OF A BETA-GLUCAN AND AN EGF RECEPTOR ANTAGONIST FOR THE TREATMENT OF CANCER AND INFECTION

(57) Abstract: The present invention encompasses a therapeutic combination composition of a β -glucan EGF receptor antagonist. This therapeutic combination composition is useful for the treatment of diseases including proliferative disorders and immune dysfunction.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2006/017065

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K36/02 A61K39/395 A61P31/00 A61P35/00
--

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/030613 A2 (UNIV LOUISVILLE RES FOUNDATION [US]; ROSS GORDON D [US]) 15 April 2004 (2004-04-15) claims page 5, line 17 - page 8, line 2 -----	1-6, 8, 11-19
X	DATABASE WPI Week 200426 Derwent Publications Ltd., London, GB; AN 2004-283158 XP002416577 & WO 2004/026341 A1 (ORIENT CANCER THERAPY CO LTD) 1 April 2004 (2004-04-01) abstract ----- -/-	1, 5, 6, 9, 11-13, 16, 18

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

25 January 2007

22/02/2007

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Böhmerova, Eva

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/017065

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEUNG N-K V ET AL: "Orally administered beta-glucans enhance anti-tumor effects of monoclonal antibodies" CANCER IMMUNOLOGY AND IMMUNOTHERAPY, BERLIN, DE, vol. 51, no. 10, November 2002 (2002-11), pages 557-564, XP002297978 ISSN: 0340-7004 abstract page 559, right-hand column, line 2 - page 560, right-hand column, line 2; figure 1 -----	1,5,6, 11-13, 16,18
X	GELDERMAN KYRA A ET AL: "Complement function in mAb-mediated cancer immunotherapy." TRENDS IN IMMUNOLOGY, vol. 25, no. 3, March 2004 (2004-03), pages 158-164, XP002416499 ISSN: 1471-4906 abstract page 162, right-hand column, last paragraph -----	1,5,6, 13,16
Y	HONG FENG ET AL: "beta-glucan functions as an adjuvant for monoclonal antibody immunotherapy by recruiting tumoricidal granulocytes as killer cells." CANCER RESEARCH, vol. 63, no. 24, 15 December 2003 (2003-12-15), pages 9023-9031, XP002416500 ISSN: 0008-5472 abstract page 9023, right-hand column, last paragraph - page 9024, left-hand column, paragraph 4 page 9030, right-hand column, paragraph 4 -----	1,5-8, 11-13, 16-18
Y	WO 94/04163 A (ALPHA BETA TECHNOLOGY [US]; JAMAS SPIROS [US]; EASSON D DAVIDSON JR [U] 3 March 1994 (1994-03-03) page 1, line 3 - line 23 page 17, line 9 - page 18, line 17 page 20, line 12 - page 21, line 17 examples 1,7,9 claims -----	1-20
Y	US 5 488 040 A (JAMAS SPIROS [US] ET AL) 30 January 1996 (1996-01-30) column 3, line 26 - column 4, line 16; examples 1,6,7 column 10, line 45 - line 60 claims -----	1-20
		-/-

INTERNATIONAL SEARCH REPORT

International application No PCT/US2006/017065

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BROWN G D ET AL: "FUNGAL BETA-GLUCANS AND MAMMALIAN IMMUNITY" IMMUNITY, CELL PRESS, US, vol. 19, no. 3, September 2003 (2003-09), pages 311-315, XP001174145 ISSN: 1074-7613 abstract page 311, right-hand column, last paragraph - page 312, left-hand column, paragraph 3 -----	1-20
Y	BOHN J A ET AL: "(1@arr 3)-beta-d-Glucans as biological response modifiers: a review of structure-functional activity relationships" CARBOHYDRATE POLYMERS, APPLIED SCIENCE PUBLISHERS, LTD. BARKING, GB, vol. 28, no. 1, 1995, pages 3-14, XP004034425 ISSN: 0144-8617 abstract page 3, right-hand column, line 9 - line 14 page 5, right-hand column, last paragraph -----	1-20
Y	US 6 217 866 B1 (SCHLESSINGER JOSEPH [US] ET AL) 17 April 2001 (2001-04-17) claims column 8, line 2 - column 9, line 19; example IX -----	1-20
Y	"Cetuximab (C225, Erbitux) in combination with irinotecan, infusional 5-fluorouracil (5-FU) and folinic acid (FA) is safe and active in patients (pts) with metastatic colorectal cancer (CRC) expressing epidermal growth factor-receptor (EGFR). Results of a phase I study" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, November 2002 (2002-11), pages S148-S149, XP004403940 ISSN: 0959-8049 abstract ----- -/-	1-20

INTERNATIONAL SEARCH REPORT

International application No PCT/US2006/017065

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KIM E S: "CETUXIMAB AS A SINGLE AGENT OR IN COMBINATION WITH CHEMOTHERAPY IN LUNG CANCER" CLINICAL LUNG CANCER, CANCER INFORMATION GROUP, DALLAS, TX, US, vol. 6, no. SUPPL 2, December 2004 (2004-12), pages S80-S84, XP009069948 ISSN: 1525-7304 page S82, right-hand column, paragraph 3 - page S83, left-hand column, paragraph 2 -----	1-20
A	GAWRONSKI MICHAEL ET AL: "Microfibrillar structure of PGG-Glucan in aqueous solution as triple-helix aggregates by small angle x-ray scattering" BIOPOLYMERS, vol. 50, no. 6, November 1999 (1999-11), pages 569-578, XP002416555 ISSN: 0006-3525 abstract page 570, left-hand column page 577, right-hand column, paragraph 1 -----	1-20
P,X	US 2006/009419 A1 (ROSS GORDON D [US] ET AL) 12 January 2006 (2006-01-12) claims paragraphs [0010] - [0020] -----	1-20
E	WO 2006/083458 A (BIORESPONSE LLC [US]; ZELIGS MICHAEL A [US]) 10 August 2006 (2006-08-10) paragraphs [0019], [0021], [0067], [0068]; claims 1,2,24 -----	1,5-8, 11-13, 16-18
E	US 2006/165700 A1 (OSTROFF GARY R [US] ET AL) 27 July 2006 (2006-07-27) claims paragraphs [0010] - [0019] -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

 International application No
 PCT/US2006/017065

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2004030613	A2	15-04-2004	AU	2003268486 A1	29-03-2004
			AU	2003295326 A1	23-04-2004
			CA	2496508 A1	15-04-2004
			CA	2496596 A1	18-03-2004
			CN	1694715 A	09-11-2005
			CN	1697659 A	16-11-2005
			EP	1536820 A2	08-06-2005
			EP	1539194 A2	15-06-2005
			JP	2006502167 T	19-01-2006
			WO	2004021994 A2	18-03-2004
WO 2004026341	A1	01-04-2004	AU	2003264488 A1	08-04-2004
			EP	1552849 A1	13-07-2005
			US	2006067947 A1	30-03-2006
WO 9404163	A	03-03-1994	AT	210450 T	15-12-2001
			AU	4095397 A	18-12-1997
			AU	679690 B2	10-07-1997
			AU	5086893 A	15-03-1994
			BR	9307104 A	30-03-1999
			DE	69331324 D1	24-01-2002
			DE	69331324 T2	22-08-2002
			EP	0655921 A1	07-06-1995
			FI	950770 A	20-02-1995
			HU	72418 A2	29-04-1996
			JP	6107702 A	19-04-1994
			JP	8500623 T	23-01-1996
			JP	2005264167 A	29-09-2005
			NZ	255857 A	28-10-1996
			PL	307567 A1	29-05-1995
			US	5783569 A	21-07-1998
			US	5622939 A	22-04-1997
US 5488040	A	30-01-1996	NONE		
US 6217866	B1	17-04-2001	NONE		
US 2006009419	A1	12-01-2006	NONE		
WO 2006083458	A	10-08-2006	NONE		
US 2006165700	A1	27-07-2006	NONE		